-Remarks-

Claims 58 and 61 are pending and were rejected in the Office Action. Claims 58 and 61 were rejected under 35 USC § 112 first paragraph and nonstatutory double patenting. Reconsideration and withdrawal of the rejections in this Office Action, mailed January 26, 2005, is respectfully requested.

I. Claim Rejections

A. § 112, First Paragraph.

Claims 58 and 61 were rejected under 35 USC § 112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicants respectfully traverse.

A detailed response is offered below which tracks Examiner's analysis of the *Wands* factors. However, in general, Applicants believe that Examiner may have missed several pertinent disclosures contained throughout the specification. Examiner's rejection frequently states that Applicants failed to demonstrate a correlation between compounds of formula (I) and the treatment of inflammatory disease. Applicants respectfully disagree and offer the following non-limiting examples. Pages 1-2 discuss the role of the presently claimed compounds in A2a receptor agonist activity and the corresponding role of neutrophil inhibition. Examiner does not refute the known role of neutrophils as mediators in inflammation. Pages 51-52 discuss an assay demonstrating the anti-inflammatory properties of compounds of formula (I). Pharmacological data corresponding to this assay is reported on page 161. In addition, Examiner has acknowledged that adenosine derivatives are known to have efficacy in treating inflammatory disease. As further discussed below, the MPEP provides that such known correlation is strongly supportive of a finding of enablement of the presently claimed invention.

Accordingly, Applicants respectfully request that Examiner reconsider and withdraw the rejection of claims 58 and 61 under 35 USC § 112, first paragraph.

1. Examiner's rejection is based upon enablement not written description

Examiner's rejection is ambiguous on its face. Examiner initially states that the rejection under § 112, first paragraph, is based upon the alleged failure to comply with the "written description" requirement. The correct point of analysis then is to determine whether the specification demonstrates possession of the claimed invention. Examiner acknowledges this construct in setting forth the present rejection on page 2 of the Office Action. However, Examiner later inexplicably switches to a discussion of enablement on page 3 of the Office Action, as follows:

> *A conclusion of lack of enablement means that, based on the evidence regarding each factor below, the specification . . . would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.*

The substantive analysis of the present rejection follows on pages 3-6 of the Office Action. Here, Examiner analyzes the *Wands* factors. Examiner correctly acknowledges these factors are probative of undue experimentation concerning enablement not written description.

Applicants conclude that the introductory points of Examiner's rejection are in error – that the present rejection is not one based on written description but rather enablement. The substantive portion of Examiner's rejection is devoted to enablement. Applicable case law plainly states that written description is a requirement distinct from enablement. Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563 (Fed. Cir. 1991), see also MPEP § 2161. Accordingly, the substantive aspects of Applicants' response to the present rejection is one based upon the "enablement" rather than the "written description" prong of § 112, first paragraph.

2. Test for enablement – undue experimentation

Under the enablement requirement, a specification must describe how to make and use the claimed invention. The test for enablement is whether a skilled person can make and use the invention without under experimentation. Factors used in determining whether a specification meets the enablement requirement include, but are not limited to,

a) breadth of claims,
b) nature of invention,
c) state of the prior art,
d) level of ordinary skill in the art,
e) predictability in the art,
f) amount of direction provided,
g) existence of working examples, and
h) quantity of experimentation needed.

See generally, 2164.01 – 2164.01(a), and In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988)(setting forth factors for determining undue experimentation, now commonly referred to as the "Wands factors.")

3. Analysis of the "*Wands* Factors" was merely cursory.

These eight factors were set forth by Examiner in issuing the present rejection. Unfortunately, Examiner's treatment of these factors was merely cursory. Applicants specification spans 161 pages of text offering numerous examples of making and using the present invention, such as, for example, making compounds of formula (I), preparing various pharmaceutically acceptable salts, solvates and compositions thereof, and using the invention to treat various conditions, including those presently claimed.

In contrast to these 161 pages, Examiner's entire substantive analysis spans only two lines, as follows:

> *It is noted that Examples 1-35 and Preparations 1-74 provide the synthesis of said compounds. The pharmacological data provided on page 161 is not sufficient.* [Office Action, page 5]

a) Examiner must explain *why* a disclosure is insufficient

Such curt analysis fails to meet the minimum burdens required of Examiner in proffering such rejections. MPEP 2164.04 describes the burden on the examiner under the enablement requirement as follows.

> *[I]t is incumbent on the Patent Office. . . to explain why it doubts the truth or accuracy of any assertion in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement.* (MPEP 2164.04, citing In re Marzocchi, 439 F.2d 220, 224 (CCPA 1971)(emphasis in original).

Simply put, Examiner's analysis falls far short of meeting this burden.

Apparently also lost in this analysis is the fact that Examiner actually acknowledges the enablement of making the compounds of formula (I) in the above cited text. Unfortunately, this acknowledgement fails to inform any other portions of Examiner's analysis. Examiner's failure to communicate this subject matter as enabled runs afoul of additional provisions of 2164.04 which call on examiner's to look for enabled subject matter and to communicate the same to applicants wherever possible.

4. Making and Using the Claimed Invention Is Taught Throughout the Specification.

Enablement of the claimed invention is found throughout the specification. The specification totals 161 pages in length. Examiner's failure to conduct any substantive examination of these numerous disclosures failed to meet the required burden as set forth in the MPEP, as discussed in Section 3(a) above. As Examiner failed to meet even this initial burden, Applicant is required to do no more. The points raised under each *Wands* factor are merely summary. Examiner failed to consider the "evidence as a whole" as required under a plain reading of the MPEP and the *Wands* decision itself.

Nevertheless, in the interest of furthering this prosecution, Applicants provide various non-limiting exemplary disclosures from the specification for the purpose of better informing Examiner's analysis upon the reconsideration of this rejection as requested by Applicants.

In general, among others, methods of making compounds of formula (I) are taught in Examples 1-35 and Preparations 1-74. Preparation of pharmaceutically acceptable salts is taught on page 51. Pharmaceutically acceptable excipients, diluents, and carriers are taught on page 52-53. Solid dosage forms are taught on page 52. Exemplary dosage ranges for tablet forms are taught on pages 53-54. Parenteral administration is taught on page 53. Intranasal administration is taught on pages 54-55. Suppositories, lotions and creams, among others applications, as well as dermal and transdermal applications are taught on page 55.

Examiner's assertion that the present application fails to teach the skilled person how to make and use the present invention simply cannot stand. Methods and examples of making compounds of formula (I), as well as pharmaceutically acceptable salts, solvates, and compositions thereof, as well as exemplary dosages and dosage forms are provided throughout.

Unfortunately Examiner failed to consider the sufficiency of any particular disclosure exemplified above. Accordingly, no further discussion on those aspects is warranted here. Consideration of the conclusions raised by Examiner under the various *Wands* factors is provided below.

a) Quantity of Experimentation

Examiner asserts that Applicants' specification fails to provide any disclosure of experimentation correlative of treating a mammal having an inflammatory disease and that the absence of such data would require the skilled artisan to engage in undue experimentation to treat such a subject.

Applicants respectfully traverse.

The anti-inflammatory properties of the compounds of formula (I) are taught on pages 51-52, among others. Such properties were evaluated by the ability of compounds of formula (I) to inhibit neutrophil function indicating A2a receptor agonist activity. Surprisingly, Examiner acknowledged Applicants teaching with respect to pharmacological data on page 161, which was based on the experiments reported on pages 51-52. Examiner stated that the data provided on page 161 was insufficient without stating why, nor separately acknowledging or discussing the sufficiency of the supporting disclosure provided on pages 51-52. Applicants encourage Examiner to re-visit this portion of the specification again.

As Examiner's allegations concerning lack of disclosure with respect to the anti-inflammatory properties of the claimed invention are directly rebutted above, Applicants respectfully request that Examiner reconsider and withdraw the present rejection.

b) Guidance Provided

Examiner states that the specification fails to provide adequate guidance concerning the amount of adenonsine derivative of formula (I) in a method for treating inflammatory disease.

Applicants respectfully traverse.

Section 2164.01(c) reminds that it is not necessary to specify the dosage if it is known in the art that such information could be obtained without undue experimentation. In spite of this, Applicants do indeed provide various dosage ranges dependent upon chosen administration forms and other factors. For example, the General Example on pages 52-53 provides a dosage range for tablet formulations of about 0.01 to 500 mg of active compound. More generally, a range of 0.00001 to 100 mg/kg, preferably 0.001 to 100 mg/kg, of compounds of formula (I) are provided on page 54 of the specification. This same section also states that determination of the appropriate dosage range is within one of ordinary skill in the art (e.g., a physician). Such declarations must be accepted as true unless Examiner can offer evidence to the contrary.

As Examiner's allegations concerning lack of disclosure with respect to dosage ranges are also directly rebutted above, Applicants respectfully request that Examiner reconsider and withdraw the present rejection.

c) Working Examples in the Specification

Examiner alleges that the examples in the specification are not sufficient to support the breadth of the claims for treating inflammatory disease. Examiner acknowledged that methods of making the compounds are described in Examples 1-35 and Preparations 1-74 but opined that the pharmacological data provided was not sufficient. No other reason or analysis regarding this alleged insufficiency was provided.

Applicants respectfully traverse.

Such cursory allegations by Examiner fail under section 2164.04, as further discussed in section 3(a) above. Nevertheless, Applicants submit that the representative number of examples adequately support the claimed genus. Examiner does not allege otherwise. Applicants are uncertain why Examiner believes that the pharmacological data is not sufficient.

Applicants remind that actual pharmacological data is not required. All that is required is a demonstration of a reasonable correlation between the activity and the asserted use. MPEP 2107.03, citing Nelson v. Bowler, 626 F2d 853, 857 (CCPA 1980). Such a "reasonable correlation" is readily provided in Applicants' specification. Pages 1-2 discuss that purine derivatives in accordance with the present invention act as selective, functional agonists of the human adenosine A2a receptor and that stimulation of A2a receptors is reported to inhibit neutrophil function. It goes on to remind that activated neutrophils release reactive oxygen species (e.g., superoxide anion radicals) and granule products (e.g. human neutrophil elastase) which act as mediators of inflammation. Such a teaching alone, without more, would be sufficient to demonstrate a reasonable correlation under MPEP § 2107.03. However, Applicants also describe an assay on pages 51 and 52 of the specification demonstrating the ability of compounds of formula (I) to inhibit neutrophil function indicating A2a receptor agonist activity. Pharmacological data from this assay was reported on page 161 of the specification.

Examiner's terse conclusion that such data is simply "insufficient" cannot be maintained. The present application indeed contains numerous working examples correlative to the claimed invention. Accordingly, Applicants request that Examiner reconsider and withdraw this rejection.

d) Nature of Invention / State of the Art

Examiner's characterization of the nature of invention and state of the art under *Wands* actually support a finding of enablement of the present invention. Examiner acknowledges that,

> *It is known in this art that certain adenosine derivatives have efficacy in treating specific conditions having an inflammatory disease.* [Office Action, page 5].

This acknowledgement supports enablement of the present invention. Again turning to § 2107.03, the MPEP reminds that courts have routinely found that evidence or acknowledgement of structural similarity between a claimed compounds and a compound with known therapeutic or pharmacological utility is supportive of an assertion that the claimed compound shares this same utility. See also In reJolles, 628 F.2d 1322 (CCPA 1980). Accordingly, Examiner's acknowledgement of recognition in the art of the anti-inflammatory properties of adenosine derivatives supports that finding enablement of the same utility for the compounds that are presently claimed.

In both the nature of invention and state of the art sections, Examiner cites Olsson *et al.* J. Med. Chem. 1986, 29(9), pages 1683-1689, to show the state of the art.

Accordingly, Applicants request that Examiner reconsider and withdraw this rejection.

e) Predictability of the Art

In this section, Examiner summarily proclaims that the extrapolation of data presented in the disclosure for the treatment of inflammatory disease is not supported in the art. Examiner offers no evidence nor cites any reference in support of this conclusion.

Examiner's statement is not supported by Applicants disclosure and Examiner's own admissions. Applicants have demonstrated above that the present disclosure adequately describes the inhibition of neutrophil function with compounds of formula (I). Neutrophil are known mediators in inflammatory response. Examiner has acknowledged that adenosine derivatives are known to have efficacy in treating inflammatory disease in discussing the fourth *Wands* factor, the nature of the invention in the present Office Action. Such evidence does not support Examiner's conclusion here that the art does not recognize the compounds of formula (I) for the treatment of inflammatory disease.

Accordingly, Applicants request that Examiner reconsider and withdraw this rejection.

f) Breadth of the Claims

Examiner reaches no conclusion within this section of the Office Action. No analysis is provided. Examiner merely recites the breadth of the claims. No response is required by Applicants.

g) Relative Skill in the Art

In this section Examiner summarily concludes that the amount of experimentation needed would be "voluminous and unduly burdensome in view of the teachings of the instant disclosure." Examiner offers no further guidance or analysis upon which to support such a conclusion.

Applicants respectfully traverse.

Applicants have demonstrated the adequate and abundant teachings throughout the specification concerning making and using the claimed invention. Examiner is referred to the prior discussion in section 4 of this response for additional details and exemplary disclosures.

Applicants have demonstrated that the presently claimed invention is fully enabled, adequately teaching the skilled practioner how to make and use the claimed invention. Applicants submit that analysis of the various *Wands* factors discussed above readily support a conclusion of enablement. Accordingly, Applicants respectfully request that Examiner reconsider and withdraw the rejection of claims 58 and 61 under 35 USC § 112, first paragraph.

B. <u>Non Statutory Double Patenting</u>

Examiner also rejected claims 58 and 61 under the judicially created doctrine of obviousness-type double patenting over claims 46, 47 and 53 of US Patent No. 6,753,322 (the '322 patent) and claims 8, 9 and 11 of US Patent No. 6,525,032 (the '032 patent). Examiner alleges that claims of the '322 and '032 patent overlap with claims of the present application.

Applicants respectfully traverse.

The present application is a divisional of US Patent Application Serial No. 09/874,007, which issued as the '322 patent. An obviousness-type double patenting rejection over this parent case cannot be maintained. The structure of formula I in the '032 patent is not the same as formula (I) in the present application.

Accordingly, Applicants respectfully request that Examiner reconsider and withdraw this rejection of claims 58 and 61 under the judicially created doctrine of obviousness-type double patenting over claims of the '322 and '032 patents.

II. Information Disclosure Statement

Applicants received a copy of an Information Disclosure Citation attached to the present Office Action with references initialed by Examiner. However, Examiner did not initial any of the references contained in the "Foreign Patent Documents" section of this form. Applicants respectfully request that Examiner initial these references and return a corrected form A820 to Applicants indicating these revisions.

-Conclusion-

Applicants, having responded to all points and concerns raised by Examiner, believe this application to be in condition for allowance. An early and favorable action is respectfully requested.

Respectfully submitted,

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